

**R E M A R K S**

**Status of the Application**

Claims 1 and 3-18 are pending in the present application.

Claim 17 has been cancelled, and Claims 1, 9, 10, 15, and 16 have been amended, to better define one embodiment of the invention, notwithstanding Applicant's belief that the cancelled and unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, but rather for the purpose of furthering Applicant's business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).<sup>1</sup> None of the amendments to the claims is related to the statutory requirements of patentability unless expressly stated so herein. No amendment made herein was intended to narrow the scope of any of the amended claims within the meaning of *Festo*.<sup>2</sup>

In particular, Claim 17 has been cancelled to avoid potential duplication of amended Claim 16.

Claims 1, 10, and 16 have been amended to elect a single species of cells in response to the Restriction Requirement which was mailed on July 3, 2001. In particular, Claims 1, 10 and 16 have been amended by deleting the recitation that the cells are "selected from FRTL-5 cells, CHO-R cells, and CHOLuc cells," and replacing it with the recitation of "CHO-Rluc cells." A typographical error has also been corrected by deleting the term "CHOLuc" cells and replacing it with the correctly spelled "CHO-Rluc" cells.

Claims 9 and 15 have been amended to correct a typographical error by changing their dependency from Claims 7 and 10, to Claims 8 and 14, respectively, in order to provide antecedent basis for the term "Stimulation Medium" which is recited in Claims 9 and 15.

These amendments do not introduce new matter.

Claims 1 and 3-18 have been rejected on the following grounds:

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<sup>1</sup> 65 Fed. Reg. 54603 (September 8, 2000).

<sup>2</sup> *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) (en banc) (Nov. 29, 2000).

1. Claims 1 and 10-18 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness; and

2. Claims 1 and 3-18 were rejected under 35 U.S.C. §103 for alleged obviousness over Evans *et al.* in view of Yamashiro *et al.*

Applicant believes that the present amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

**1. Rejection Of Claims 1 And 10-18 Under 35 U.S.C. §112, Second Paragraph**

Claims 1 and 10-18<sup>3</sup> stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness on the ground that the claims recite "CHO-Luc" cells "while it appears from their specification that they intended to claims CHO-Rluc cells."<sup>4</sup> Applicant has corrected this inadvertent typographical error to reflect the correct "CHO-Rluc cells." Accordingly, withdrawal of this rejection is respectfully requested.

**2. Rejection Of Claims 1 And 3-18 Under 35 U.S.C. §103 Over Evans *et al.* In View Of Yamashiro *et al.***

Claims 1 and 3-18 were rejected under 35 U.S.C. §103 for alleged obviousness over Evans *et al.*<sup>5</sup> in view of Yamashiro *et al.*<sup>6</sup> Applicant respectfully traverses because a *prima facie* case of obviousness is not established, and is in fact rebutted by the cited references' teachings.

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<sup>3</sup> Applicant notes that the Examiner inadvertently rejected Claim 2, which is not pending. From the substance of the rejection, Applicant assumes that the Examiner intended this rejection to apply to pending Claim 1 rather than to cancelled Claim 2.

<sup>4</sup> Office Action, page 2, item 3.

<sup>5</sup> Evans et al. (1999) "Development of a luminescent bioassay for thyroid stimulating antibodies," J. Clin. Endocrin. Metabolism 84(1)374-377.

<sup>6</sup> Yamashiro et al. (1999) "Mechanism of the Augmentative Effect of High Polyethylene Glycol (PEG) Concentrations on the Thyroid Stimulating Activity in TSAAb-IgG Using a Porcine Thyroid Cell Assay," Endocrine Research 25:67-75.

The Examiner is respectfully reminded that he must establish a *prima facie* case of obviousness by citing to a combination of references which (a) suggests or motivates one of skill in the art to combine the claim elements to yield the claimed combination, and (b) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish **either one** of these requirements precludes a finding of a *prima facie* case and, without more, entitles Applicant to withdrawal of the rejection based on obviousness.<sup>7</sup> The Examiner has not fulfilled his burden with respect to either of these two requirements.

**A. A Motivation To Combine The References Is Lacking**

In setting out the premise of alleged motivation, the Examiner stated that "[t]he claimed invention differs from the prior art teaching(s) by the recitations of exposing said cells to a stimulation medium *after* exposing said cells to said test sample, wherein said stimulation medium comprises PEG."<sup>8</sup> However, Applicant notes that this premise is incorrect since this sequence of exposure to the test sample and to the PEG-containing Stimulation Medium is recited in only Claims 9 and 15. None of the remaining claims recite such a sequence of exposure.

The Examiner next argued that "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to add PEG to the assay taught by Evans *et al.*, because the addition of PEG to a cAMP assay for the detection of TSAb in test samples increased cAMP production by eight fold, as taught by Yamashiro *et al.*, thereby making the assay more sensitive."<sup>9</sup>

However, rather than providing motivation, Yamashiro *et al.* **teaches away** from substituting Evans *et al.*'s CHO-Rluc cells for its porcine thyroid cells because Yamashiro *et al.* demonstrates that the effect of PEG on a particular biological response in porcine thyroid cells **does not correlate** with a similar biological response in Evans *et al.*'s CHO-Rluc cells.

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<sup>7</sup> MPEP §2143; *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

<sup>8</sup> (Emphasis added) Office Action, page 3, second paragraph.

<sup>9</sup> Office Action, page 3, third paragraph.

The Examiner is respectfully reminded that the law is clear that a **teaching away** from the claimed invention alone can **defeat** obviousness.<sup>10</sup> In the instant case, Evans *et al.* discloses incubating CHO-Rluc cells with sera from Graves' Disease patients and using these cells in a luminescent assays to detect thyroid stimulating antibodies (TSAb). Unlike the claimed methods, the Evans *et al.* methods do not employ PEG in the medium. Yamashiro *et al.* discloses that inclusion of PEG with porcine thyroid cells that are incubated with TSAB-IgG results in stimulating production of cAMP by the cells.

Importantly, Yamashiro *et al.* differs from the claimed invention in, among other things, using porcine thyroid cells rather than the recited CHO-Rluc cells. Importantly also, Yamashiro *et al.* shows that PEG had **no effect** on the cAMP levels in porcine thyroid cells which were treated with bovine thyroid stimulating hormone (bTSH).<sup>11</sup> In sharp contrast, the instant Specification demonstrates that PEG **"significantly and substantially enhanced"** the cAMP levels in the recited CHO-Rluc cells which were treated with bTSH.<sup>12</sup> This **contradictory** cAMP response to bTSH which was shown by Yamashiro *et al.*'s porcine thyroid cells in the presence of PEG, as compared to the recited CHO-Rluc cells in the presence of PEG, **teaches away** from incubating Evans *et al.*'s CHO-Rluc cells with

Yamashiro *et al.*'s PEG because Yamashiro *et al.*'s data shows that the biological response of porcine thyroid cells in the presence of PEG is **opposite** to the biological response of the recited CHO-Rluc cells in the presence of PEG. Taken one logical step further, and applying the observed **divergent** effect of PEG on the different cell types' response to the recited "thyroid stimulating autoantibodies" (rather than to Yamashiro *et al.*'s TSH), the artisan would **expect** that Yamashiro *et al.*'s observed enhancement of the cAMP response to thyroid

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<sup>10</sup> *Winner International Royalty Corp. v. Wang*, 53 USPQ2d 1580, 202 F.3d 1340, 13449 (Fed. Cir. 2000), citing *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

<sup>11</sup> Yamashiro *et al.*, Figure 1A and 1B, middle columns. Also, "no stimulatory effect of 5% PEG on bTSH was observed." Yamashiro *et al.*, Abstract. Also, "the increase in cAMP production by PEG was specific for TSAb as no stimulation was observed by other thyroid simulators such as TSH." Yamashiro *et al.*, page 71, last paragraph.

<sup>12</sup> Specification, page 38, lines 12-14; Table 3, third and fourth columns.

stimulating antibodies (TSAb) in the presence of PEG<sup>13</sup> would be correlated with an **opposite** effect in CHO-Rluc cells. In other words, the artisan would expect from Yamashiro *et al.*'s data that PEG would have **no effect** on the response of **CHO-Rluc cells** to the recited **thyroid stimulating autoantibodies (TSAb)**. Because the artisan is taught that there is **no advantage** (*i.e.*, no effect) with respect to the cell's response to the recited TSAb when adding PEG to CHO-Rluc cells, there can be **no motivation** that Evans *et al.*'s cells be combined with Yamashiro *et al.*'s PEG.

Because Yamashiro *et al.*'s teaching away negates a motivation to combine the references, a *prima facie* case of obviousness must fail.

**B. A Reasonable Expectation Of Success Is Not Established**

The Examiner's singular statement with respect to this essential prong of a *prima facie* case of obviousness is that "from the teachings of the references, it is *apparent* that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention."<sup>14</sup> However, this statement suffers from the following problems.

**i. The Examiner's Position Is Unsupported**

First, the Examiner's statement is not supported by **any** evidence or scientific reasoning. The law is that:

"Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence."<sup>15</sup>

Because the Examiner's conclusory statement falls afoul of the legal requirement for evidentiary support, it *ipso facto* cannot establish a reasonable expectation of success in practicing the claimed invention.

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<sup>13</sup> Yamashiro *et al.*, Figure 1A and 1B, right columns.

<sup>14</sup> (Emphasis added) Office Action, page 3, second full paragraph.

<sup>15</sup> *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), citing *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993) and *In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977).

Second, the Examiner's statement is based on the improper assumption that the Examiner knows what would be "apparent" to one of ordinary skill in the art. However, the Examiner is **not** "one skilled in the art."<sup>16</sup> Furthermore,

"if the rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported when called for by the applicant, by an affidavit from the examiner."<sup>17</sup>

Because the Examiner's views regarding the alleged obviousness of the presently claimed methods are unsupported by evidence or by an affidavit showing facts within the Examiner's knowledge, then the Examiner's views cannot enter into the determination of obviousness.

**ii. Success In One Species Does Not Reasonably  
Predict Success With Another Species**

Even if the Examiner were to search for evidence supporting a reasonable expectation of success, such a search would be futile for the following legal and factual reasons.

Referring first to the legal standard, the Federal Circuit has stated that a single showing of success in **one species** would **not** lead one of ordinary skill to believe that it applied to **another species**, but rather would amount to nothing more than an invitation to experiment.<sup>18</sup> Thus, under the law, even if the artisan used Evans *et al.*'s **CHO-Rluc cells** in place of Yamashiro *et al.*'s **porcine thyroid cells** which are incubated with PEG, such substitution would **not** lead one of ordinary skill reasonably to believe that the results observed with Yamashiro *et al.*'s **species of porcine thyroid cells** would predict similar success with the **different species of the recited CHO-Rluc cells**.

As to the facts, the effect of PEG on the ability of the recited CHO-Rluc cells to detect TSA<sub>b</sub> could not reasonably have been predicted because Yamashiro *et al.* uses porcine thyroid cells which are from a **different animal** (porcine versus hamster), **different tissue** (thyroid versus ovary), and which are **not genetically engineered** (versus the genetically engineered CHO-Rluc cells which express human TSH receptor). Each of these variables

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<sup>16</sup> *Stratoflex, Inc. v. Aroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

<sup>17</sup> MPEP 2144.03.

<sup>18</sup> *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

alone (let alone in combination) would argue against the artisan's reasonable prediction that the recited CHO-Rluc would respond similarly to PEG as did Yamashiro *et al.*'s porcine thyroid cells.

**iii. Yamashiro *et al.* Teaches Away From A Reasonable Expectation Of Success**

The Examiner is again respectfully reminded that a teaching away from the claimed invention alone can defeat obviousness.<sup>19</sup> Not only does Yamashiro *et al.* teach away from a **motivation** to combine the references (as discussed *supra*), but it also teaches away from any alleged reasonable **expectation of success** when substituting Evans *et al.*'s CHO-Rluc cells for Yamashiro *et al.*'s porcine thyroid cells. As explained above, Yamashiro *et al.* teaches the artisan to expect that PEG would have **no effect** on the response of CHO-Rluc cells to the recited thyroid stimulating antibodies (TSAb). However, this expectation is **contradicted** by the instant Specification's data which shows that, in direct disagreement with Yamashiro *et al.*'s prediction, PEG **"significantly and substantially enhanced"** the cAMP levels in CHO-Rluc cells in response to Graves IgG.<sup>20</sup>

Not only was the instant Specification's result unexpected because it was contrary to Yamashiro *et al.*'s prediction, but its unexpected nature is also further evidenced by Yamashiro *et al.*'s express statement that "the precise mechanism of the stimulating effect of PEG on cAMP production into PTC [*i.e.*, porcine thyroid cells] by TSAb-IgG is *unclear*."<sup>21</sup> Because Yamashiro *et al.* **did not know the mechanism** which was responsible for their results with the porcine thyroid cell type, one of skill in the art could not have reasonably predicted whether or not this unknown mechanism also was operative in the recited CHO-Rluc cells, and therefore could not reasonably have predicted whether the recited CHO-Rluc cells would have responded similarly or differently from Yamashiro *et al.*'s cells in the presence of PEG.

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<sup>19</sup> *Winner International Royalty Corp. v. Wang*, 53 USPQ2d 1580, 202 F.3d 1340, 13449 (Fed. Cir. 2000), citing *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

<sup>20</sup> Specification, page 38, lines 12-14; Table 3, last column.

<sup>21</sup> (Emphasis added) Yamashiro *et al.*, page 74, second full paragraph.

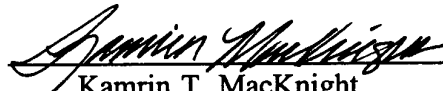
Because the instant inventor proceeded without guidance from, but rather contrary to the expectation of, Yamashiro *et al.*, and because the inventor **empirically** determined that PEG has the **superior property** of enhancing the sensitivity of CHO-Rluc cells to thyroid-stimulating antibodies, any alleged expectation of success is refuted. This alone precludes a *prima facie* case of obviousness.

In sum, not one, but **two** of the prongs of a *prima facie* case of obviousness stand unestablished and rebutted. Since absence of just **one** of these prongs necessitates withdrawal of the rejection based on obviousness, it is respectfully requested that the rejection of Claims 1 and 3-18 under 35 U.S.C. § 103 be withdrawn.

**Conclusion**

All grounds of rejection and objection of the Office Action of October 23, 2001 having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (415) 904-6500.

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**APPENDIX I**  
**MARKED-UP VERSION OF REWRITTEN, ADDED,**  
**AND/OR CANCELLED CLAIMS**

**COPY OF PAPERS  
ORIGINALLY FILED**

The following is a marked-up version of the claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Brackets denote deleted text, and underlining denotes added text.

**IN THE CLAIMS**

Cancel Claim 17.

Amend Claims 1, 9, 10, 15, and 16 as follows:

1. (Twice Amended) A method for determining the presence of thyroid-stimulating autoantibodies in a test sample, comprising:
  - a) providing:
    - i) a test sample suspected of containing thyroid-stimulating autoantibodies,
    - ii) cultured CHO-Rluc cells [selected from FRTL-5 cells, CHO-R cells, and CHOLuc cells], wherein said cultured cells are contained within a testing means, and
    - iii) polyethylene glycol;
  - b) exposing said test sample to said cultured cells and said polyethylene glycol under conditions such that said thyroid-stimulating antibodies are detectable; and
  - c) observing for the presence of detectable thyroid-stimulating antibodies.
  
9. (Once Amended) The method of Claim [7] 8, wherein said Stimulation Medium comprises said polyethylene glycol.

10. (Once Amended) A method for determining the presence of thyroid-stimulating autoantibodies in a test sample, comprising:
- a) providing:
    - i) a test sample suspected of containing thyroid-stimulating autoantibodies,
    - ii) cultured CHO-Rluc cells [selected from the group consisting of FRTL-5 cells, CHO-R cells, and CHOLuc cells] contained within a testing means, and
    - iii) polyethylene glycol;
  - b) exposing said test sample to said cultured cells and said polyethylene glycol under conditions such that said thyroid-stimulating antibodies are detectable; and
  - c) observing for the presence of detectable thyroid-stimulating antibodies, wherein said observing utilizes a luminometer.
15. (Once Amended) The method of Claim [10] 14, wherein said Stimulation Medium comprises said polyethylene glycol.
16. (Once Amended) A method for determining the presence of thyroid-stimulating autoantibodies in a test sample, comprising:
- a) providing:
    - i) a test sample suspected of containing thyroid-stimulating autoantibodies,
    - ii) cultured CHO-Rluc cells [selected from the group consisting of FRTL-5 cells, CHO-R cells, and CHOLuc cells] contained within a testing means,
    - iii) Growth Medium, and
    - iv) Stimulation Medium, wherein said Stimulation Medium comprises polyethylene glycol;
  - b) exposing said cultured said to said Growth Medium to produce grown cells;

- c) exposing said test sample to said grown cells and said Stimulation Medium under conditions such that said thyroid-stimulating antibodies are detectable; and
- c) observing for the presence of detectable thyroid-stimulating antibodies, wherein said observing utilizes a luminometer.